Fred Hutch Cancer Center

UW Medicine

16th ANNUAL COMPREHENSIVE HEMATOLOGY & ONCOLOGY REVIEW

CONSULTATIVE HEMATOLOGY

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October 9, 2025

Land Acknowledgement

Fred Hutchinson Cancer Center acknowledges the Coast Salish peoples of this land, the land which touches the shared waters of all tribes and bands within the Duwamish, Puyallup, Suquamish, Tulalip and Muckleshoot nations.

OBJECTIVES

KNOW THE COMMON INDICATIONS FOR A HEMATOLOGY CONSULTATION

•

EXPLORE THE DIFFERENTIAL DIAGNOSES FOR ROUTINE BLOOD COUNT ABNORMALITIES

•

ILLUSTRATE THE UTILITY OF AN EXPERT CONSULTATIVE SERVICE IN DIAGNOSING RARE HEMATOLOGIC DISEASES

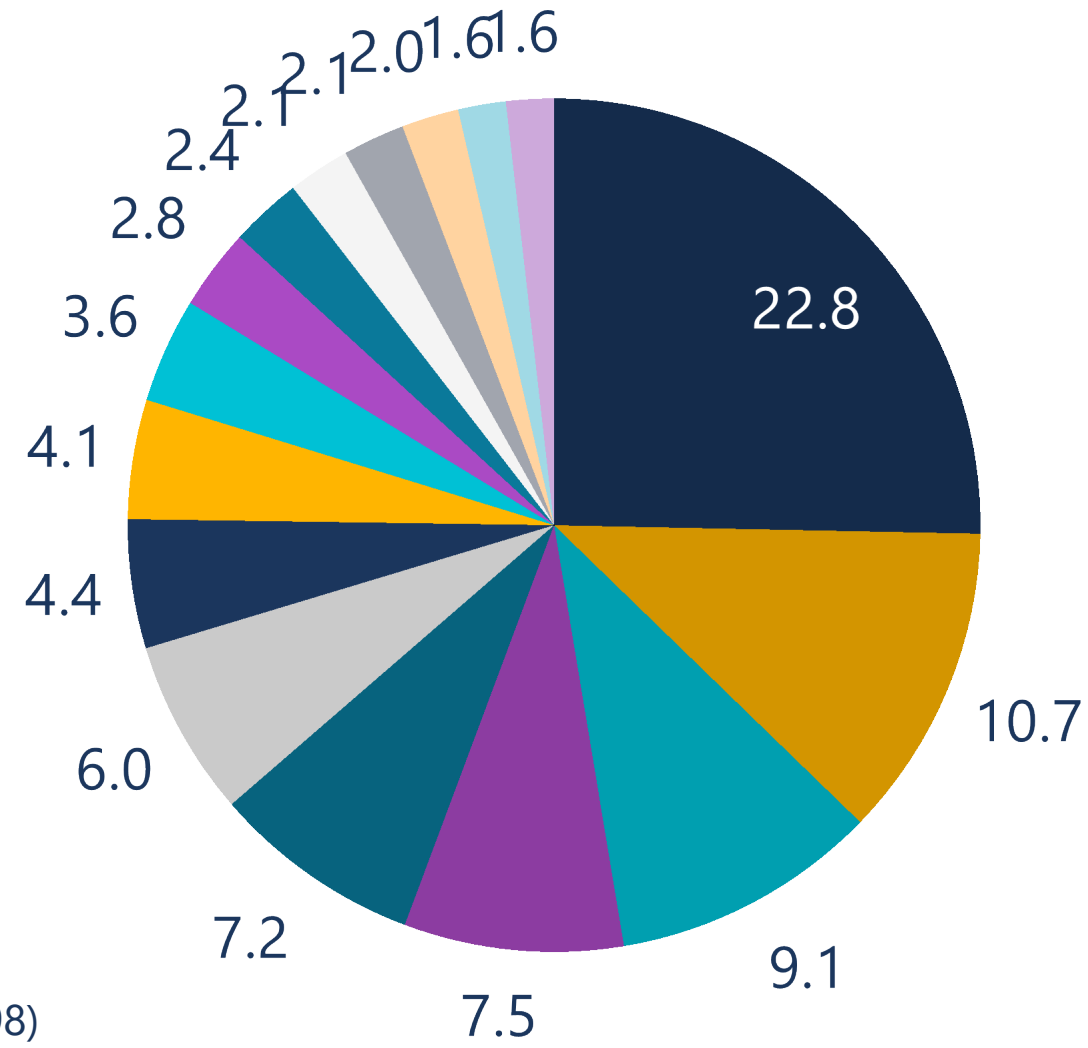
DISCLOSURES

I have no disclosure or conflicts of interest

ACKNOWLEDGEMENT

Nicholas Burwick, MD

REASONS FOR CONSULT REQUEST TO HEMATOLOGY



(N=598)

Burwick N, Unpublished data

HEMATOLOGISTS AS DIAGNOSTICIANS

Table 2. Avoided Visit Rates and Primary Reason for e-Consult Across Specialties*

Variable	Specialty				
	Psychiatry (*n* = 891)	**Infectious Disease (*n* = 1634)**	**Hematology (*n* = 2216)**	**Rheumatology (*n* = 287)**	**Dermatology (*n* = 1484)**
Avoided visits 120 d after e-consult, *n (%)*†	825 (92.6)	1432 (87.6)	1926 (86.9)	187 (65.2)	919 (61.9)
Primary reason for e-consult (based on subset manually reviewed), *n/N (%)*‡					
Diagnosis	2/145 (1.4)	58/149 (38.9)	102/150 (68)	130/147 (88.4)	50/150 (33.3)
Therapy	135/145 (93.1)	87/149 (58.4)	46/150 (30.7)	17/147 (11.6)	85/150 (56.7)
PCP education	4/145 (2.8)	1/149 (0.7)	2/150 (1.3)	0/147 (0)	9/150 (6.0)
Patient inquiry	4/145 (2.8)	3/149 (2.0)	0/150 (0)	0/147 (0)	6/150 (4.0)

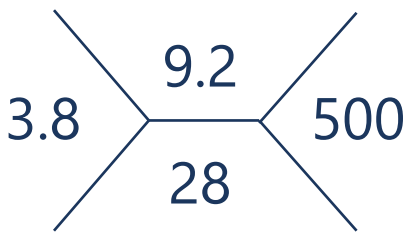
e-consult = electronic consultation; PCP = primary care physician.
* Percentages may not sum to 100 due to rounding.
† Defined as lack of in-person visit referral within 120 d of placement of e-consult order.
‡ A subset of medical records (150 from each of the 5 specialties; 9 records were missing) was manually reviewed to assess the primary reason for e-consult.

Ahmed S e al. Ann Int Med 2020

Case 1: Iron-refractory anemia

38-year-old woman with anemia, felt likely related to history of menstrual blood loss

You are consulted after her anemia fails to respond to 3 months of ‘twice daily’ oral iron supplements

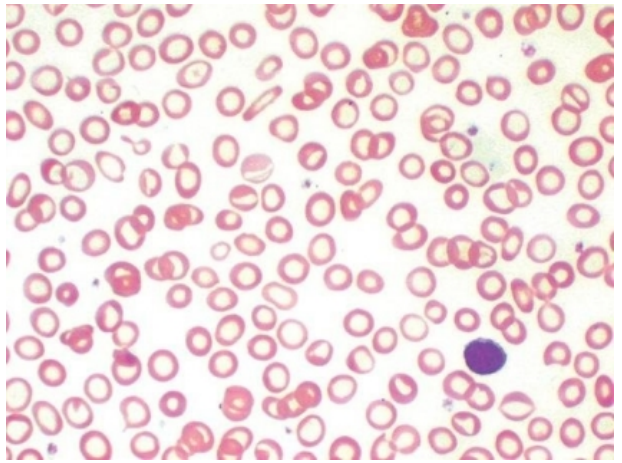


3 months
oral iron

MCV 72 fL
TSat 12%
Ferritin 15 ng/mL
TIBC 410 µg/dL
Corrected retic 0.8%

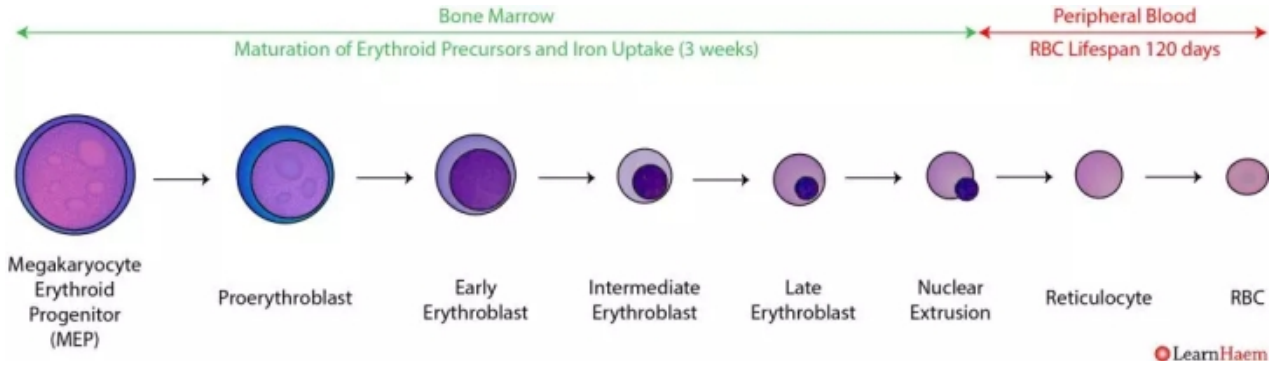
MCV 70 fL
TSat 10%
Ferritin 10 ng/mL
TIBC 420 µg/dL
Corrected retic 0.8%

Peripheral smear:



Microcytic hypochromic RBCs

DIFFERENTIAL DIAGNOSIS OF 'IRON REFRACTORY' ANEMIA



While not strictly defined, a hemoglobin rise <1g/dL after 4-6 weeks of oral iron repletion is suboptimal; warrants further clinical assessment

Differential Diagnosis

- Continued excessive iron loss
- Iron intolerance/non-adherence
- Impaired absorption
- Impaired utilization [inflammatory block]
- Inherited disorder [IRIDA/mutations in TMPRSS6]

COMMON CONDITIONS IN PATIENTS WITH ANEMIA REFRACTORY TO ORAL IRON

Diagnosis	Autoimmune gastritis	*H pylori**	Menorrhagia	Gastrointestinal lesions	Celiac	Negative
n (%)	77 (26)	57 (19)	96 (32)	31 (10)	14 (5)	21 (7)
Mean age ± 1 SD, y	41 ± 16	37 ± 19	39 ± 10	60 ± 14	39 ± 14	33 ± 13
Gender, M/F	14/63	17/40	0/96	13/18	3/15	2/21
Main diagnosis alone	26	57	39	21	11	21
H pylori	39	—	57	10	2	0
Menorrhagia	11	0	—	0	1	0
Gastrointestinal lesions	1	0	0	—	0	0
Aspirin or NSAID	9	3	1	7	0	1
Refractory to oral iron, %	69	68	38	47	100	10

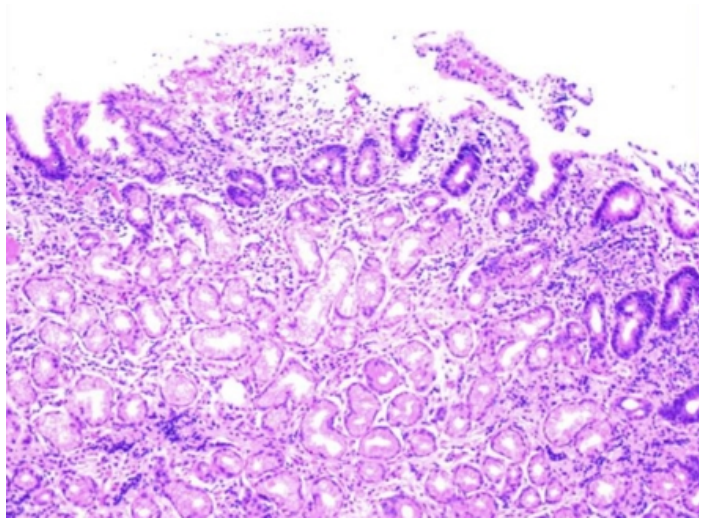
Main diagnostic categories and coexistent findings in 300 consecutive IDA patients referred for hematologic evaluation (Hershko et al[15]).
*One hundred sixty-five total *H pylori*.

Hershko C et al. Blood 2014

Patient reports having abdominal discomfort for the past 6 months, which had worsened since starting the iron pills. Because of these symptoms, she also began taking a daily over-the-counter proton pump inhibitor

Fecal occult blood test: positive

Normal colonoscopy, but EGD demonstrates *H. pylori* gastritis



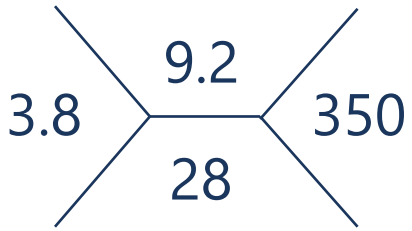
Case 2: Microcytic anemia

25-year-old man from India with anemia. No history of anemia in the past. Normal CBC 1 year ago.

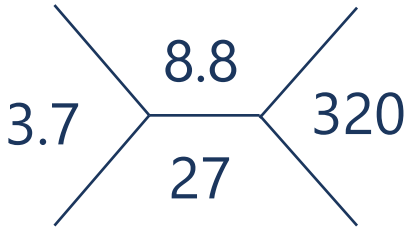
CBC, 6 months ago: Hgb 9.2 g/dL, MCV 72 fL. Corrected retic 0.8%

Iron profile: TSat 25%, TIBC: 380 µg/dL. Ferritin 120 ng/mL

You are consulted for evaluation of microcytic anemia. He was prescribed oral iron (ferrous sulfate 325 mg every other day)



6 months
Oral Iron

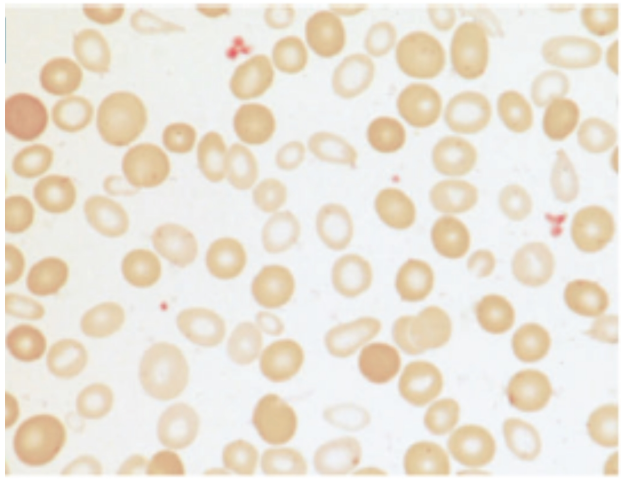


MCV 72 fL
TSat 25%
Ferritin 125 ng/mL
TIBC 380 µg/dL
Corrected retic 0.8%

MCV 70 fL
TSat 35%
Ferritin 215 ng/mL
TIBC 370 µg/dL
Corrected retic 0.8%

Additional lab results:
Normal CRP and ESR
Normal hemoglobin electrophoresis
Normal alpha globin DNA sequencing

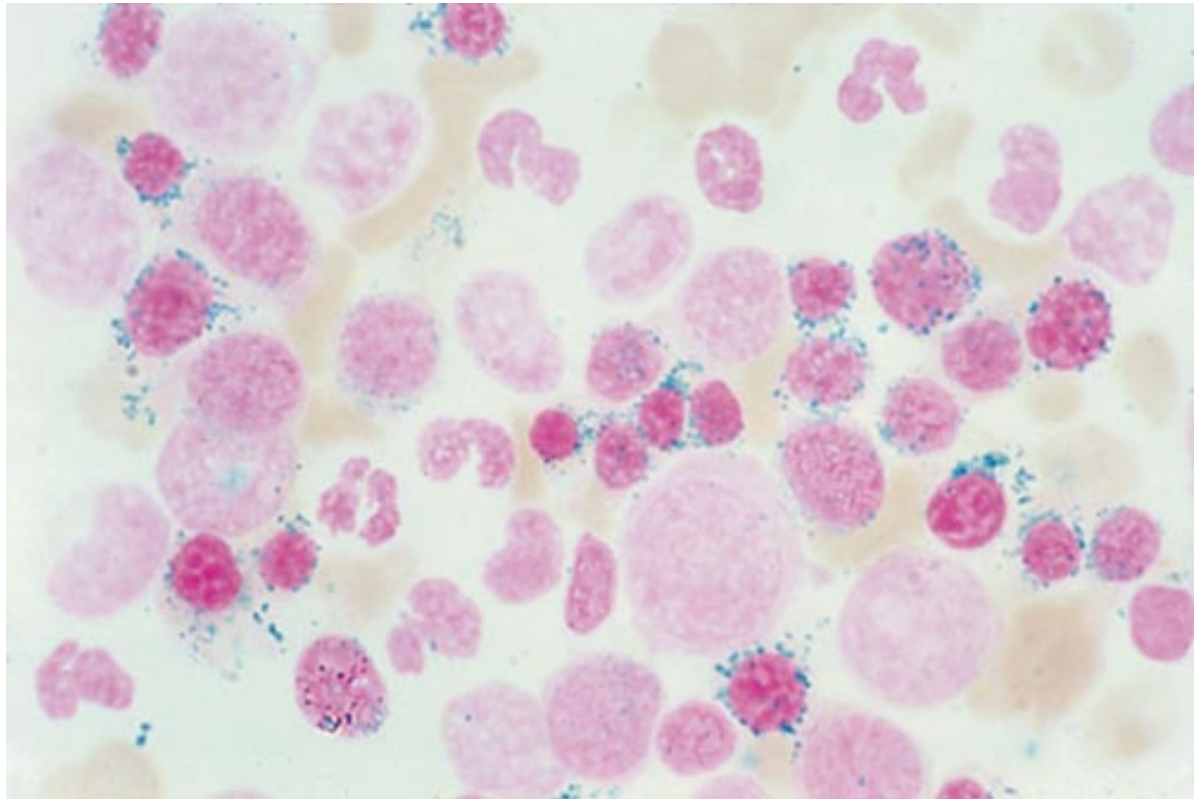
Peripheral smear



Dimorphic population of macrocytes
and hypochromic microcytic RBCs

Cazzola M Haematologica 2011

Bone marrow aspirate with iron stain



Prussian blue stain demonstrating ringed sideroblasts

Cazzola M Haematologica 2011

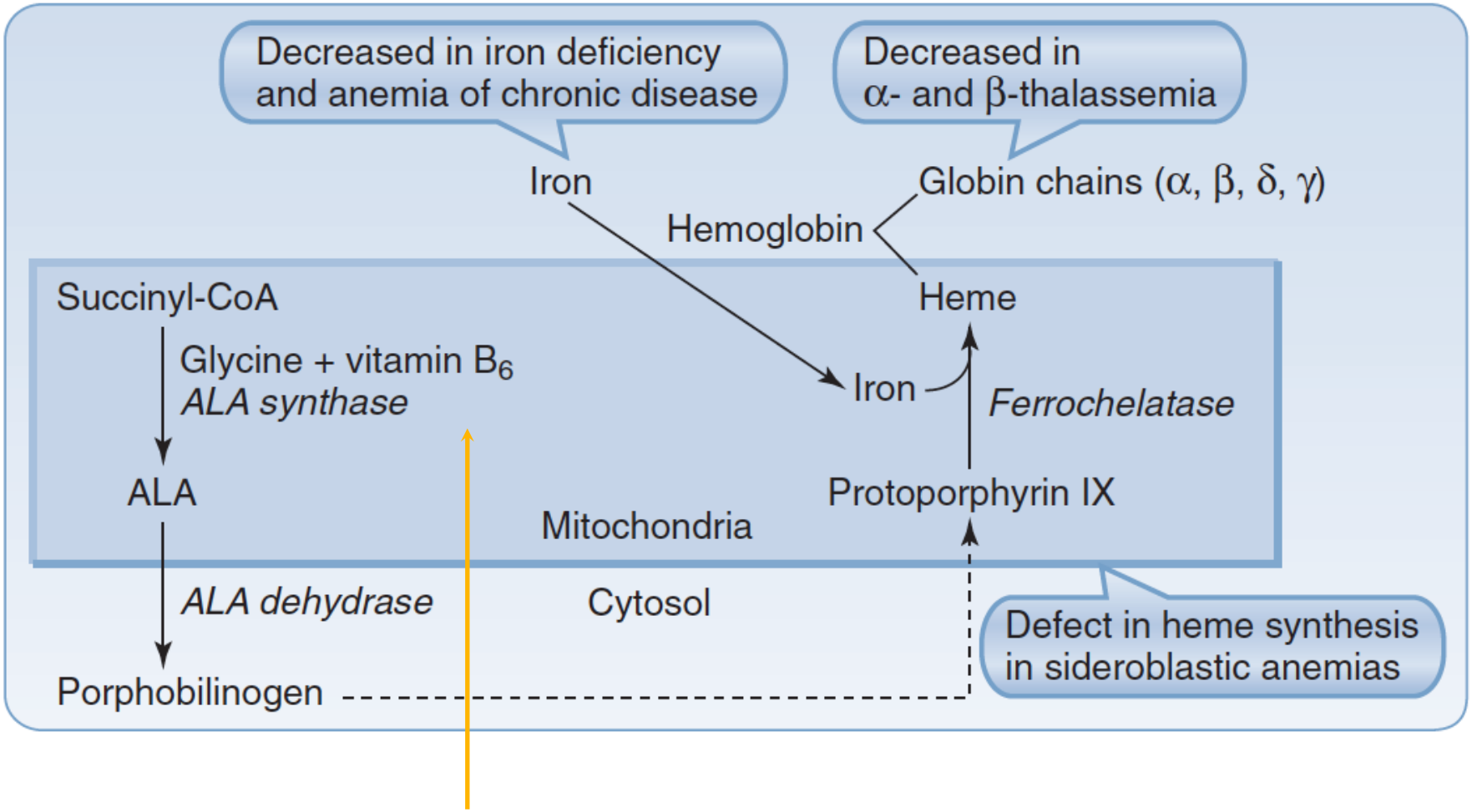
CAUSES OF SIDEROBLASTIC ANEMIA

Congenital:
X-linked mutations in *ALAS2*, or other mutations which impact heme biosynthetic or metabolic pathways

Acquired:
Clonal: Myelodysplasia with ringed sideroblasts (+/- thrombocytosis)

Metabolic:
Copper Deficiency (Zinc excess)
Drugs (isoniazid, linezolid)
Excessive alcohol use
Hypothermia

Patient reports he started isoniazid (INH) for tuberculosis prophylaxis 1 year ago



INH depletes vitamin B6 (pyridoxine)

Case 3: Chronic macrocytic anemia

55-year-old man with history of relapsing polychondritis and fevers, poorly responsive to glucocorticoid therapy and oral methotrexate.

He has been off methotrexate for 6 months, but the rheumatologist notices that the patient has a persistent macrocytic anemia

10.2

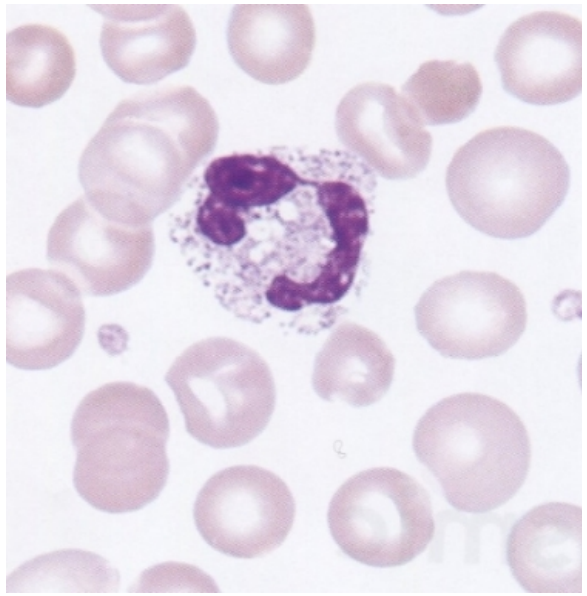
7.7 104

30

MCV 119 fL

Corrected Retic: 0.9%

Peripheral blood smear

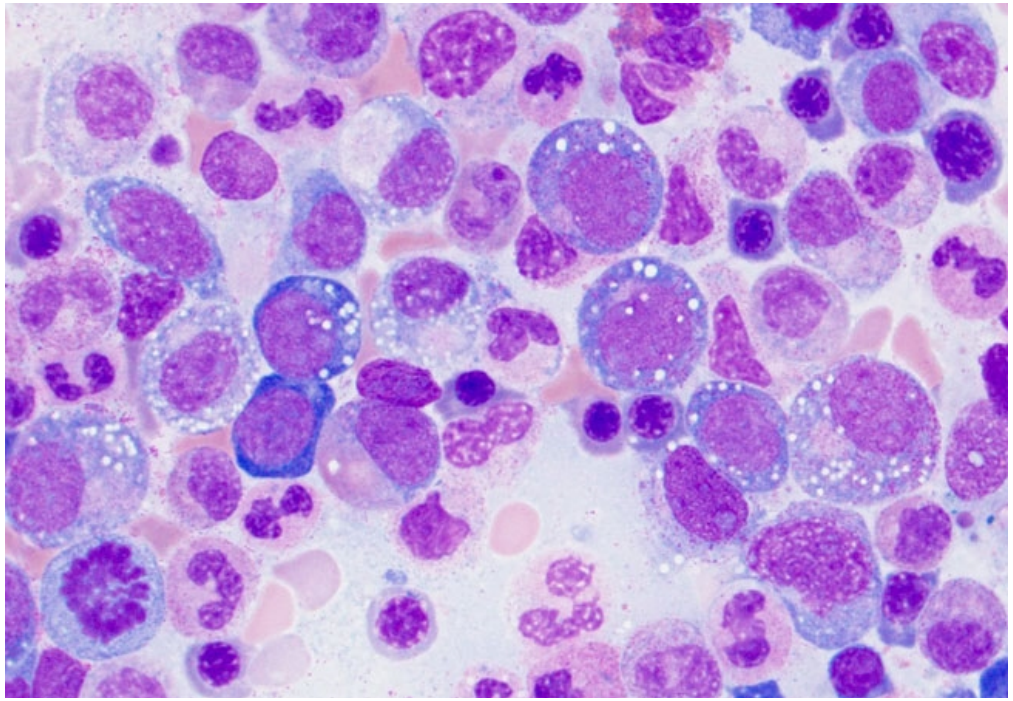


Macrocytes and neutrophils with toxic granulations and cytoplasmic vacuoles

Additional lab results:

Vitamin B12: 807 pg/mL
Folic acid >20
Copper: 94 µg/mL (normal)
CRP/ESR: **elevated**
Ferritin: **945 ng/mL**
Normal LFTs, TSH
Denies ETOH

Bone marrow evaluation



Erythroid and megakaryocytic atypia with cytoplasmic vacuoles in erythroid precursors. No overt dysplasia. Blasts 2%.

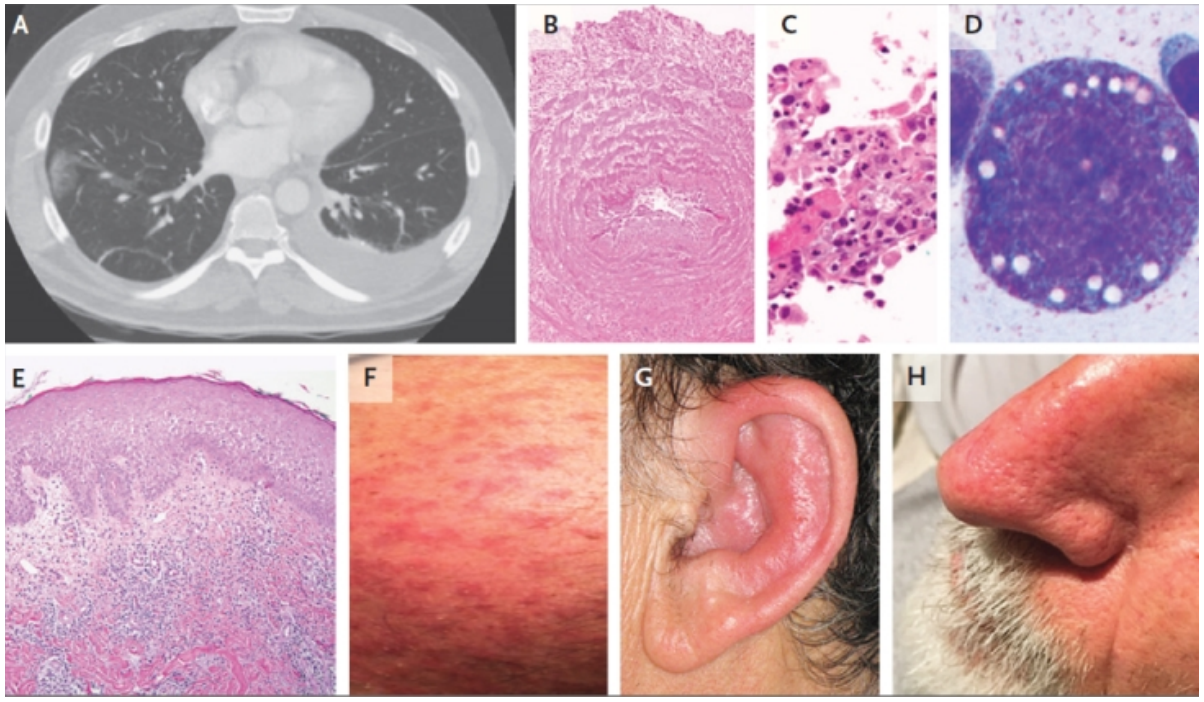
Normal MDS FISH panel and cytogenetics
Myeloid NGS gene panel negative

? Drug/toxin
? Infection/inflammation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease



Vacuoles
E1 enzyme (*UBA1*)
X-linked
Auto-inflammatory
Somatic

Key clinical features

Fever — no. (%)	23 (92)
Skin involvement — no. (%)†	22 (88)
Pulmonary infiltrate — no. (%)	18 (72)
Ear and nose chondritis — no. (%)	16 (64)
Venous thromboembolism — no. (%)	11 (44)
Macrocytic anemia — no. (%)	24 (96)
Bone marrow vacuoles — no./total no. (%)	18/18 (100)

***UBA1* mutation was detected**

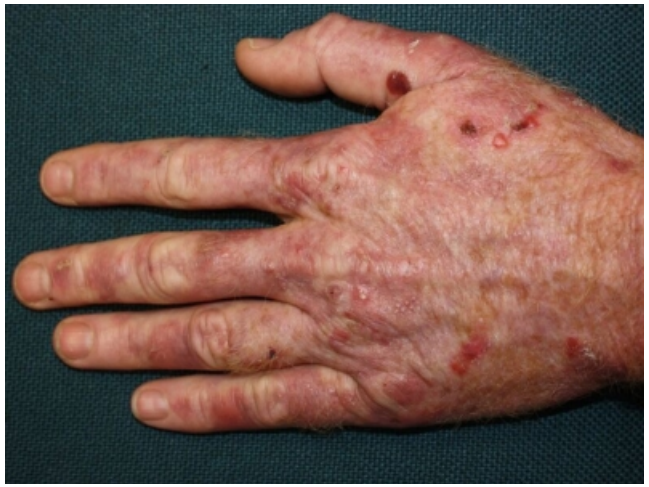
Beck DB et. al. NEJM 2020

Case 4: Photosensitive skin rash and anemia

45-year-old male presents with painful blisters on the hands.
He has a history of EtOH use and chronic hepatitis C.

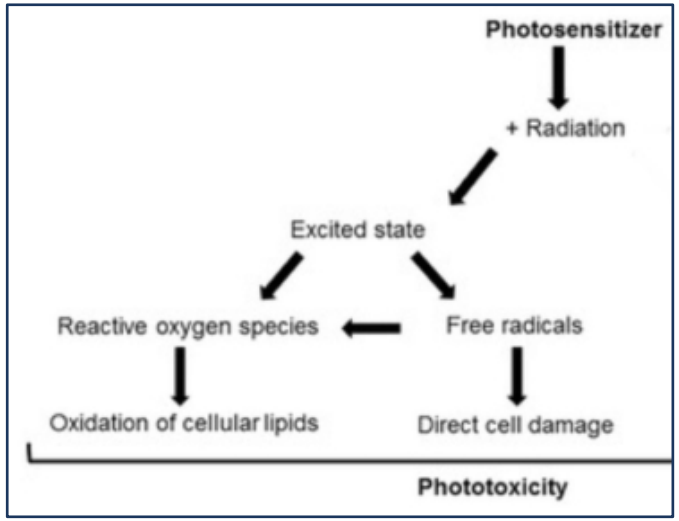
CBC: Hgb: 11 g/dL and PLTs: 115 k/µL

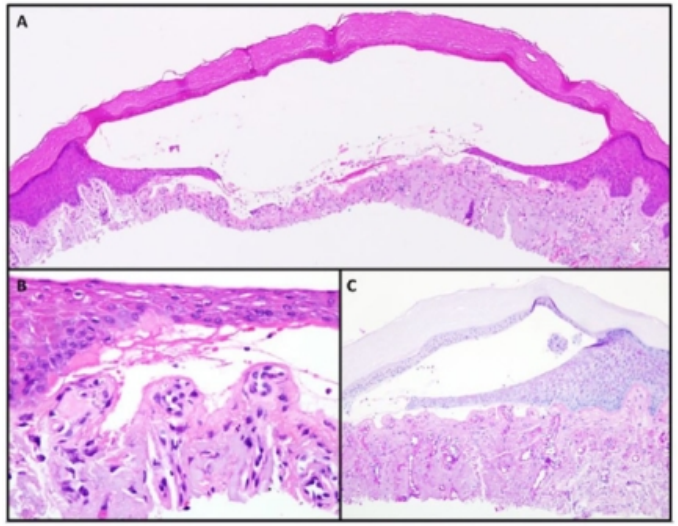
Ferritin: 545 ng/mL, iron saturation: 35%
HFE DNA screen is negative
ALT: 45 U/L, normal AST



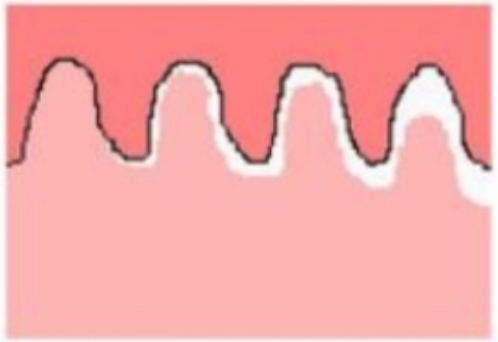
Blistering skin lesions, sun exposed skin

Source: stat pearls: acute porphyria



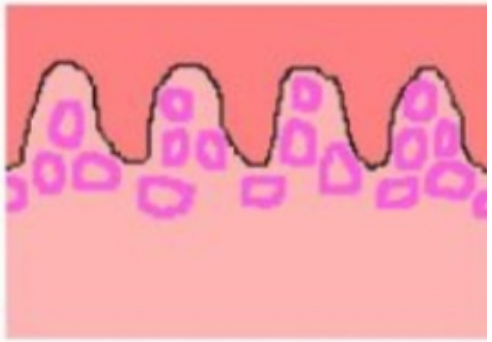


Skin Histopathology in Porphyria



Subepidermal blister formation with preservation of the shape of the dermal papillae

Variegate / Cutanea Tarda



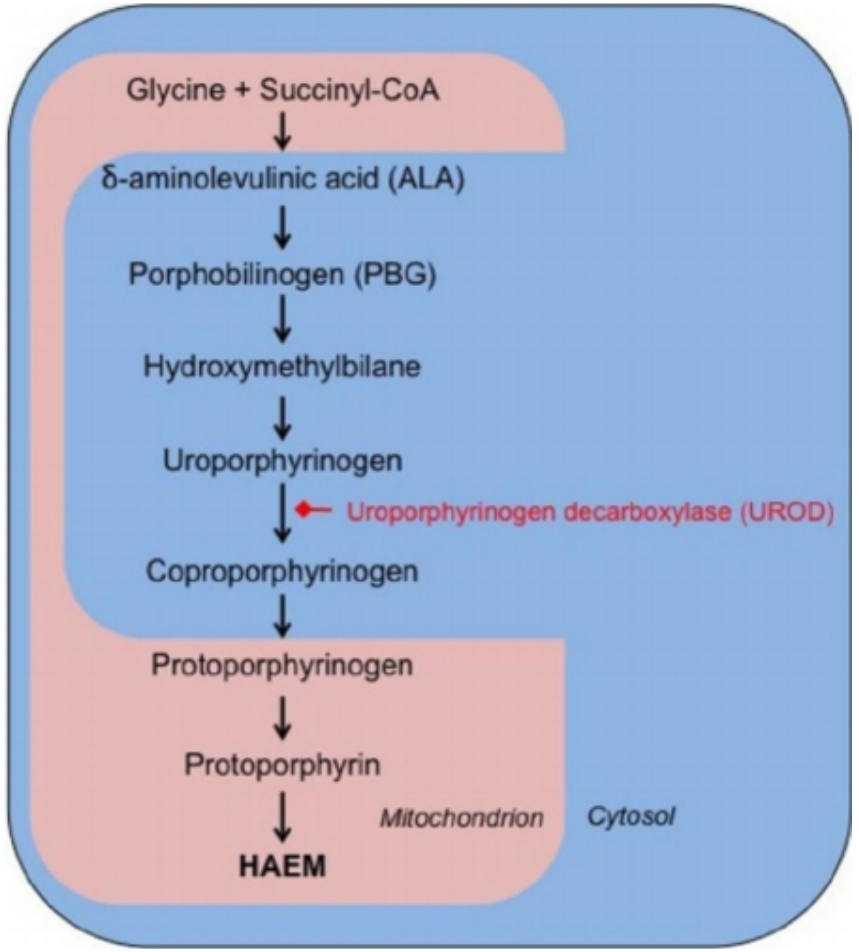
Intensely PAS-positive material deposited thickly around the blood vessels

Erythropoietic Protoporphyria

EPP: non-blistering photosensitivity

Hofmann GA et al. Dtsch Dermatol Ges 2021
Singh M et al. J Investigative Medicine 2019

PCT: INHERITED OR ACQUIRED DEFICIENCY OF UROD



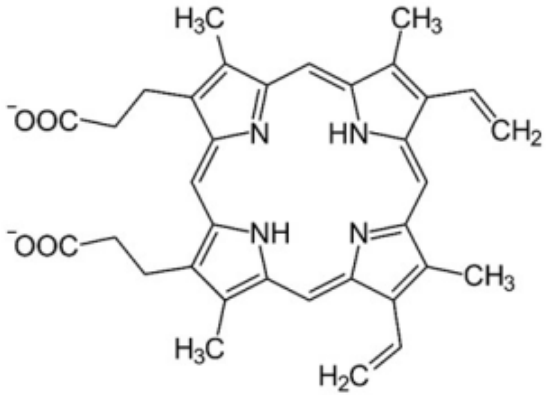
- Iron dependent UROD inhibition (hepatic specific)
- Low UROD activity (<20%)
- Build up of water-soluble uroporphyrins
- Porphyrins detectable in urine

- Risk factors: Hep C, EtOH, Hemochromatosis

- Treatment with phlebotomy (ferritin <50) or low dose hydroxychloroquine (100 mg twice weekly) can be effective

Plakke M et al. BMJ Case Reports 2013

EPP: DEFICIENT ACTIVITY OF FERROCHELATASE

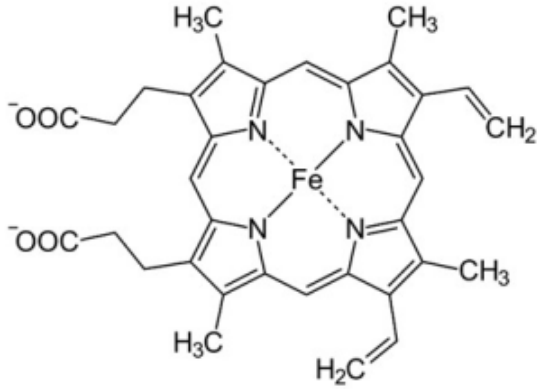


Protoporphyrin IX (PPIX)

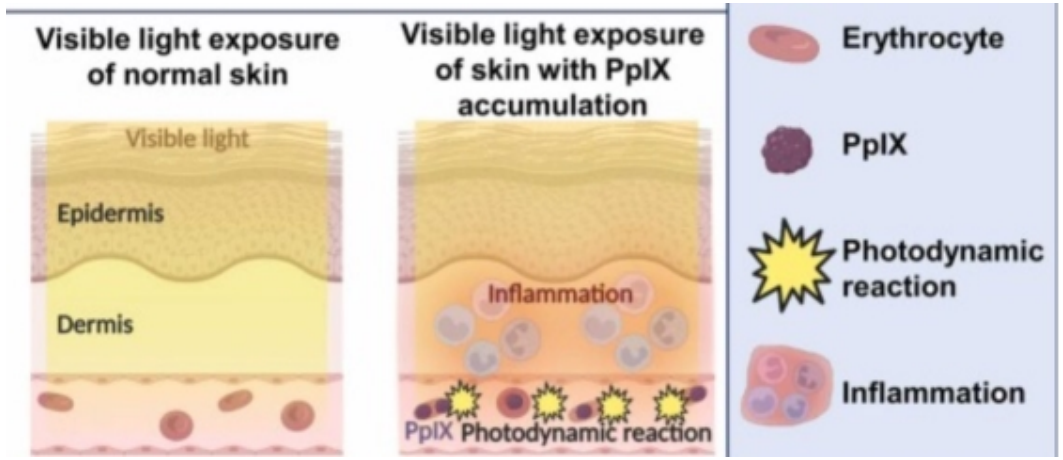
Ferrochelatase

Fe^{++}

Zinc incorporated when Fe++ unavailable



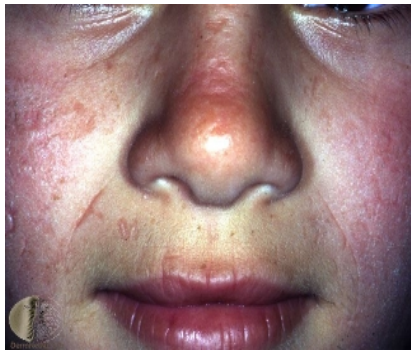
Heme



EPP: accumulation of lipid soluble Metal-free protoporphyrin (PPIX)

Immediate photosensitivity on exposure to visible light

No porphyrins in urine



ASH Image Bank 2013; 17944.

Case 5: **Erythrocytosis**

48-year-old man is being evaluated by primary care for erythrocytosis.

Hematocrit is 58% with an elevated serum erythropoietin and negative JAK2V617F DNA test.

He smokes 1-2 cigarettes per day. He has no history of chronic obstructive lung disease or obstructive sleep apnea.

You are asked if additional hematologic work-up is needed?

DIFFERENTIAL DIAGNOSIS FOR ERYTHROCYTOSIS

Congenital:
EPOR mutations
VHL mutations (Chuvash polycythemia)
High oxygen affinity hemoglobin
Other mutations

Relative Polycythemia:
Volume contraction: dehydration, diuretics

Secondary (compensatory):
Chronic obstructive lung disease
Obstructive sleep apnea
Chronic carbon monoxide
High altitude living
Right-to-left cardiac shunt
Obesity-hypoventilation syndrome

Acquired:
Polycythemia vera (JAK mutations)
Other myeloproliferative neoplasms
Hepatocellular or renal cell carcinoma
syndromes: POEMS, TEMPI
Renal artery stenosis
Post-Kidney Transplant

Medications/Drugs:
Testosterone/anabolic steroids
ESAs
Luspatercept
SGLT-2 inhibitors (empagliflozin)
Autologous blood doping

Lab results:

- Hgb: 18.4 g/dL, Hct: 58%
- WBC and PLT normal
- JAK2 variants: not detected
- Erythropoietin: **54 IU/L** (normal: 4-21)
- Chest X-Ray: Normal
- Pulmonary function test: Normal
- Sleep study: Normal
- Carboxyhemoglobin **2.7%**
- Hgb-O2 affinity: 26 mmHg (normal: 26-29)

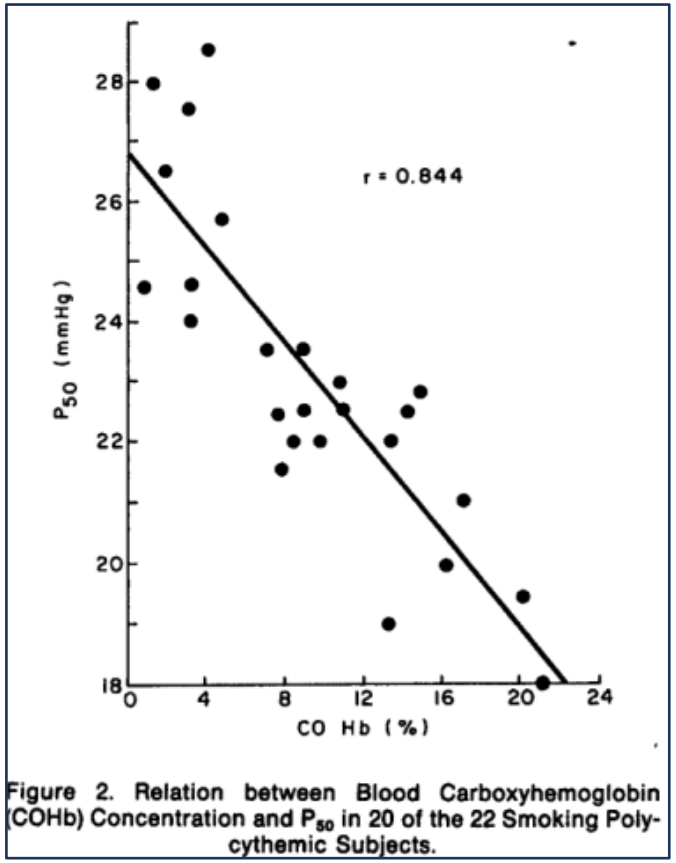


Figure 2. Relation between Blood Carboxyhemoglobin (COHb) Concentration and P_{50} in 20 of the 22 Smoking Polycythemic Subjects.

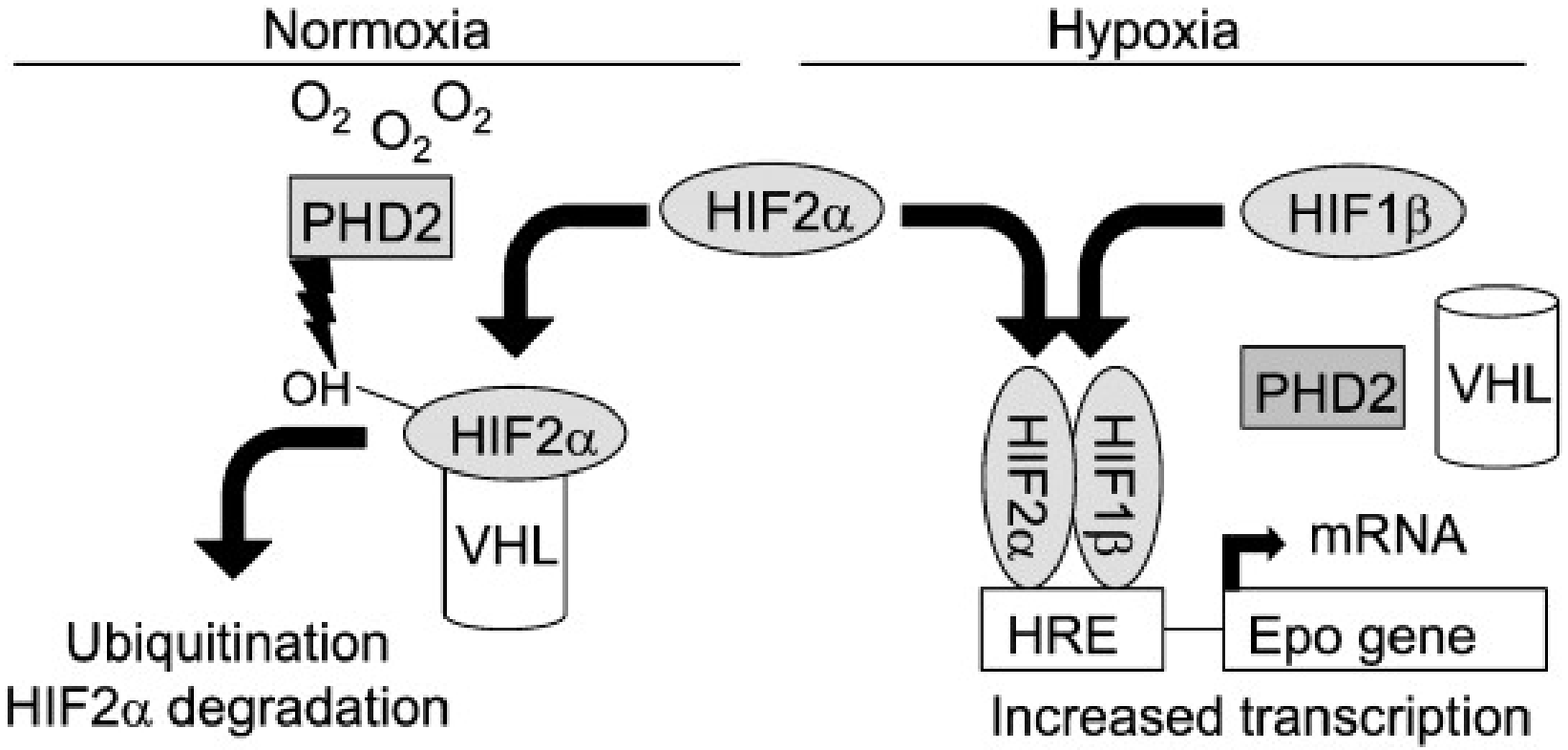
Lower P50 = left shift of Hgb-oxygen dissociation curve

Non-smokers: Average P50 26.7 (0.6% carboxy-hgb)

Smith RJ NEJM 1978

How cells sense and adapt to oxygen availability

LOW OXYGEN ENVIRONMENTS STIMULATE *EPO* TRANSCRIPTION

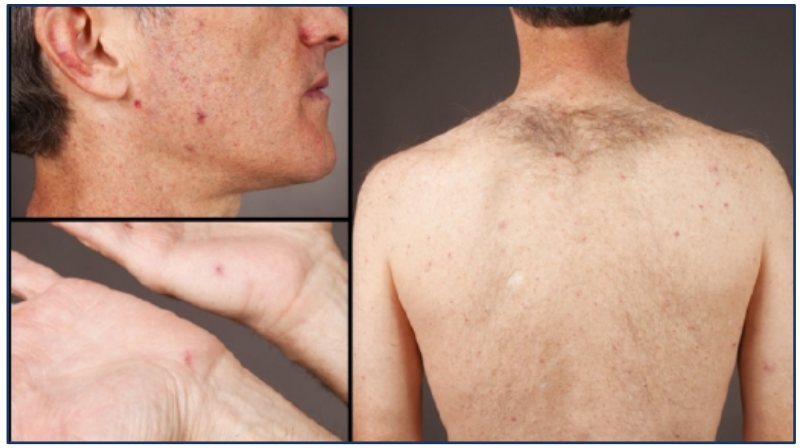


Lee G et al. European J Internal Med 2015

The patient returns 1 year later, after pursuing an observational approach.

He was able to quit smoking, but he reports increasing fatigue and headaches.

He has noticed a 15 lb weight loss and new skin lesions.



Hematocrit: 62%
S. erythropoietin 2,400 IU/L

?? Epo secreting tumor

Sykes DB et al. Blood 2020

TUMOR ASSOCIATED ERYTHROCYTOSIS

Infrequently observed; seen in 1-5% of **renal cell carcinomas**, and 3-12% of **hepatocellular carcinomas**.

Also seen in **cerebellar hemangioblastoma, pheochromocytoma, uterine leiomyomas**

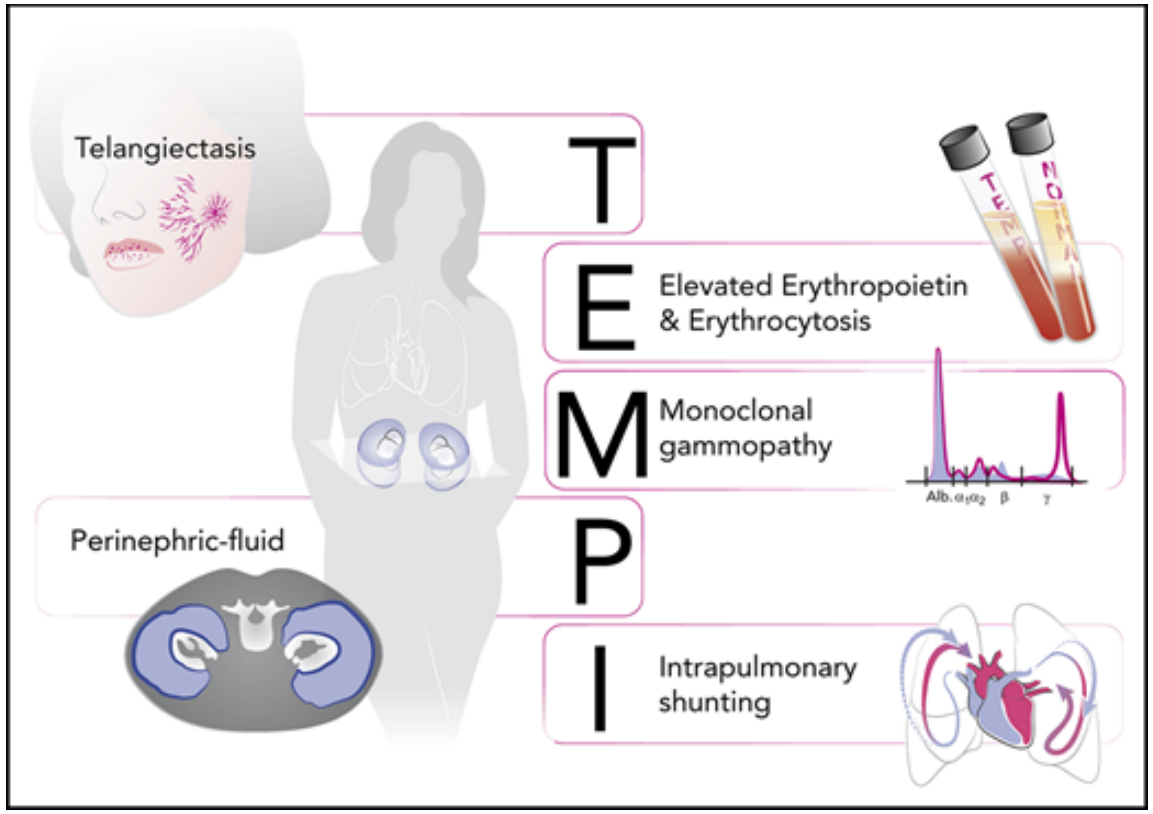
Mechanism of paraneoplastic erythrocytosis:

- **Hypoxia**: Tumors may create a hypoxic environment, stimulating EPO production.
- **Direct Secretion**: Some tumors can produce EPO independently of oxygen levels.

Da Silva et al. Blood 1990
Sakisaka S et al. Hepatology 1992

Chest/abdomen/pelvis CT:
No evidence of malignancy identified, but a **perinephric fluid collection** detected, without renal cysts.

SPEP demonstrates 0.7 g/dL IgG-K monoclonal protein



Sykes DB et al. Blood 2020

Question 1:

A 44-year-old female presents with iron deficiency anemia that has not improved after 6 months of oral iron repletion. What laboratory test result would best support a primary defect in heme biosynthesis?

A) Positive *h. pylori* stool antigen
B) Ringed sideroblasts in bone marrow
C) Hemochromatosis HFE gene mutation
D) Increased hemoglobin A2

Question 1:

A) Positive *h. pylori* stool antigen

B) Ringed sideroblasts in bone marrow

C) Hemochromatosis HFE gene mutation

D) Increased hemoglobin A2

Answer choice B is the correct answer.

Ringed sideroblasts detected by Prussian blue stain on bone marrow specimens reflect the presence of iron laden mitochondria encircling the erythroid nucleus. Ringed sideroblasts may be seen in association with hereditary or acquired defects in heme biosynthesis. Answer choice A is incorrect. A positive stool antigen test for h.pylori would support an impairment in iron absorption. Answer choice C is not correct since HFE gene mutations are associated with iron overload. Answer choice D is not correct because increased Hgb A2 is associated with beta thalassemia, which would impair beta globin synthesis.

Question 2:

A 65-year-old male presents with polycythemia, with a hematocrit of 58%. What test result would best support a diagnosis of compensatory polycythemia?

A) JAK2V617F DNA mutation
B) Decreased serum erythropoietin
C) Decreased hemoglobin P50
D) Hepatic mass on CT imaging

Question 2:

A) JAK2V617F DNA mutation

B) Decreased serum erythropoietin

C) Decreased hemoglobin P50

D) Hepatic mass on CT imaging

Answer choice C is the correct answer.

Decreased hgb P50 reflects a shift of the hgb-oxygen dissociation curve to the left (seen in the setting of chronic carbon monoxide exposure due to cigarette smoking and impaired oxygen delivery to tissues) resulting in compensatory polycythemia. Answer choices A and B are not correct. JAK2V617F DNA mutation and decreased serum erythropoietin would both support a diagnosis of primary polycythemia vera. Answer choice D is not correct. A hepatic mass on CT imaging could support the presence of an epo-secreting tumor.

Question 3:

Which of the following is a feature in a patient with acquired porphyria cutanea tarda ?

A. Responsiveness to vitamin B6
B. Defect in ferrochelatase activity
C. Build up of metal free protoporphyrin
D. Iron-dependent uroporphyrinogen decarboxylase inhibition

Question 3:

A. Responsiveness to vitamin B6
B. Defect in ferrochelatase activity
C. Build up of metal free protoporphyrin
D. Iron-dependent uroporphyrinogen decarboxylase inhibition

Answer choice D is the correct answer.
Iron-dependent inhibition of uroporphyrinogen decarboxylase (UROD) is a feature of acquired PCT. In acquired (sporadic) PCT, hepatic iron overload and oxidative stress lead to the formation of an inhibitor of UROD, specifically uroporphomethene, which is generated by iron-dependent oxidation of uroporphyrinogen. This inhibitor competitively impairs UROD activity, resulting in the characteristic accumulation of uroporphyrins. Answer choices A, B and C are not correct. Defect in ferrochelatase activity, build-up of metal free protoporphyrin and responsiveness to vitamin B6 are all seen in erythropoietic porphyria.

"Knowledge is a process of piling up facts; wisdom lies in their simplification."

- Martin H. Fischer

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Thank you

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